REMARKS

By this amendment, claims 25 and 27-34 are pending. Claim 26 is cancelled. Claims 25 and 27-34 are believed consonant with elected Group I of the Restriction Requirement as drawn to a method for identifying compounds that bind to a target of interest. No new matter is added by the amendments.

Rejection under 35 USC § 112, second paragraph

Claims 25-34 stand rejected under 35 USC § 112, second paragraph as allegedly indefinite. Claim 25 is allegedly vague and indefinite because the preamble does not correlate with the body of the claim. The preamble of the claim recites "a method for identifying compounds, where the body of the claim recites "detecting the non-covalent binding. It is unclear if detecting the compound to the target identifies the compound.

Claim 25, from which all claims depend, is amended to correlate detecting with identifying by insertion of a "whereby" clause which makes identification operational after detecting binding of the compound to the target. Thus the preamble correlates with the body of the claim in identifying compounds that bind to a target of interest.

Rejection under 35 USC § 102(b)

Claims 25, 26, 28 and 30 stand rejected under 35 USC § 102(e) as allegedly anticipated by Griffey et al. US 6770486, ("Griffey").

The rejection is respectfully traversed. To anticipate a claim, a single reference must contain all of the elements of that claim. In addition, the single reference must contain an enabling disclosure (Chester v. Miller, 906 F.2d 1576 (Fed. Cir. 1990). The mere disclosure of a chemical formula or class of compounds used to designate compounds does not, by itself, anticipate those compounds (In re Brown, 329 F.2d 1006 (CCPA 1964).

Claim 25 is now amended to limit a target biomolecule selected from a polypeptide and a protein. Griffey does not enable protein targets. Griffey enables only RNA as targets. Griffey provides no examples of proteins or polypeptides as target molecules. Griffey focuses on RNA as exemplary embodiments, "RNA being particularly preferred as a target molecule" (column 6, line 39). It is well known in the

art that the binding properties of RNA and proteins are different. A molecule which binds to RNA cannot be predicted to bind to any particular protein. In fact, the essence of Griffey is that finding molecules which bind to targets like RNA is difficult and requires sophisticated methods such as mass spectroscopy with mass measurements that infer kinetic data. To ascribe the methods in Griffey which are all based on RNA targets to protein targets is too uncertain and tenuous. Griffey does not enable protein targets, and thus should not be relied upon as such.

In addition, claim 25 is now amended to identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry. Support for methods of identifying a 1:1 complex may be found, among other places in the specification, at page 1, line 12; page 10, lines 16-17; page 15, lines 11-14; page 16, line 26; page 19, lines 16-18; and in particular, at page 21, lines 25-27; at page 45, lines 16-21; and at page 47, lines 6-9 and 17-20. Griffey does not teach a 1:1 complex, or a complex where one linked ligand compound is non-covalently bound to a target biomolecule. Griffey does not teach the value of screening for 1:1 complexes, which the present invention has discovered. Griffey teaches forming complexes "with the target with an affinity greater than baseline". The value or utility of establishing a baseline affinity is not disclosed in Griffey, nor does Griffey disclose how to establish a baseline affinity and what the person skilled in the art should do with it.

In contrast, the present invention teaches that optimizing linked ligand binding to target biomolecule includes selecting those which form a 1:1 ratio, i.e. where a single linked ligand molecule binds to a single target molecule. The present invention also teaches how to detect and measure 1:1 complexes. A 2:1 complex of linked ligand and target biomolecule is taught by the present invention to not be optimal. See page 25, lines 22-25.

In addition, claim 25 is now amended to limit the members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups

which form hydrophobic interactions. Support for functional groups of members of sets of ligands may be found, among other places in the specification, at: page 25, lines 6-10.

In addition, claim 25 is now amended by adding the element that the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups.

Griffey does not teach ligands with certain functional groups. Griffey does not teach ligands that have different functional groups. Griffey teaches "concatenating" ligands. Concatenating is an undefined term in Griffey. The reader is left to ponder its meaning. Not only is it vague and indefinite, Griffey does not teach how to concatenate. Griffey speaks only conceptually and prophetically about "ligand fragments that are concatenated together in a structural configuration that improves the binding properties of the fragments for the invention (column 5, lines 37-40), and "In concatenating ligands together using the methods and processes of the invention, two ligands that have mM (millimolar) affinities might be joined and yield a concatenated ligand that might have nM affinity (nanomolar) (column 14, line 66 to column 15, line 2). Griffey is full of expressions of desired outcomes and devoid of enablement. In particular here, Griffey gives no guidance on how to "concatenate" ligands to achieve greater binding affinity of linked ligand for target biomolecule. Griffey expresses only a wish, a speculation, such as "Two or more ligands can be joined by concatenation into new structural configurations to create a new ligand that will have improved binding characteristics or properties" (column 14, lines 51-53). The reader is uninformed as to: (1) how the ligands are joined, (2) what new structural configurations, and (3) what binding characteristics or properties these may be. Griffey further hopes that "Concatenation can be effected based on empirical or computational predictions" (column 14, lines 60-61). This may be so, but the reader will not learn how from Griffey. In contrast, the present invention does give definite teaching and examples of linking ligands, with examples of structural configurations, and measures their binding properties. Griffey even attempts to distract the reader from reality with ruminations about "virtual fragments of a ligand followed by virtually concatenating the selected ligand fragments together in silico to form a 3D model..." (column 5, lines 41-60).

In addition, claim 25 is now amended with the element that the linked ligand compound binds to the target biomolecule with higher affinity than the member of the first set of ligands or the member of the second set of ligands. Support for methods where the linked ligand compound binds to the target biomolecule with higher affinity than the member of the first set of ligands or the member of the second set of ligands may be found, among other places in the specification, at: page 15, lines 11-14; page 42, lines 7-11;

In addition, claim 25 is amended to include the limitations of claim 26 which is hereby cancelled.

Rejection under 35 USC § 103(a)

Claim 27 and 29 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey in view of Wells et al WO 00/00823, ("Wells").

The rejection is respectfully traversed. To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the cited art. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey or Wells teach or suggest any one of elements (i), (ii) or (iii). The cited references thus collectively fail to teach all the elements of the claimed subject material.

Furthermore, Wells does not disclose or suggest detecting by mass spectrometry the non-covalent binding of a compound to a target where the compound is formed by chemically linking two ligands which bind to the target. Since Griffey does not disclose or suggest the first binding site is the same as the second binding site, and does not enable protein targets, there is no motivation, and the Examiner has not provided any showing of a motivation, to combine these references to make obvious the claims of the present

invention. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Wells.

Rejection under 35 USC § 103(a)

Claim 31 and 34 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey in view of Hajduk et al, J. Am. Chem. Soc. 1997, 119, 5818-5827, ("Hajduk").

The rejection is respectfully traversed. To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the cited art. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey or Hajduk teach or suggest any one of elements (i), (ii) or (iii). The cited references thus collectively fail to teach all the elements of the claimed subject material. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Hajduk.

Rejection under 35 USC § 103(a)

Claim 31 and 32 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey in view of Ellman WO 99/49314, ("Ellman").

The rejection is respectfully traversed. To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the cited art. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH,

functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey or Ellman teach or suggest any one of elements (i), (ii) or (iii). Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Ellman.

Rejection under 35 USC § 103(a)

Claim 31 and 33 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey in view of Erlanson US 6919178, ("Erlanson").

The rejection is respectfully traversed. To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the cited art. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey or Erlanson teach or suggest any one of elements (i), (ii) or (iii). Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Erlanson.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to combine the prior art references. There must also be a reasonable expectation of success in combining the references to practice the claimed invention. In addition to the reasons cited above, the requisite suggestion, motivation, and expectation of success have not been demonstrated to render the present claims of the invention obvious.

Conclusion

It is believed that the amendments made here place the application in condition for allowance and should be entered. With respect to any and all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter, and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

In view of the above, reconsideration and allowance of this application are now believed to be in order. Applicants respectfully request that a timely Notice of Allowance be issued in this case. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at the number indicated below.

Respectfully submitted,
GENENTECH, INC.

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